REMARKS

The Invention

The present invention is directed to a mutant antibody comprising a reactive site not present in the wild-type of said antibody and complementarity-determining regions (CDRs) that recognize a metal chelate. The reactive site is in a position proximate to or within said complementarity-determining regions. The reactive site is the mutation and has complementary reactivity with a reactive group on the metal chelate selected from carboxyl groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups.

Status of the Claims

After entry of this amendment, claims 1-3, 10-11, 14-25, and 30-44 are pending in the above-referenced patent application. Claims 10 and 11 are deemed to be in condition for allowance. Applicants acknowledge and appreciate the Examiner's statement that claims 10 and 11 are allowable.

Claims 1, 42, and 43 have been amended to recite "reactive group on said metal chelate." Support for these amendments is found in the specification at, *e.g.*, page 63, lines 11-12. Claims 17 and 31 have been amended to recite "wherein said mutant antibody and said targeting moiety are not the same" Support for these amendments is found in the specification at, *e.g.*, page 50, line lines 11-14. Claim 21 has been amended to recite that the covalent bond between the reactive site and the reactive group is formed by "the interaction of said reactive site and a reactive functional group selected from an acryloyl moiety, a haloalkyl moiety, an alkene moiety, and an acrylamido moiety." Support for this amendment is found in the specification at, *e.g.*, page 62, line 23 to page 64, line 17, and page 74, line 20. Claim 43 has been amended solely for clarity to recite "regions" in lieu of "region regions." Thus, no new matter has been introduced by these amendments.

In the present Office Action, the pending claims were rejected, in various combinations, under 35 U.S.C. § 112, first paragraph, under 35 U.S.C. § 112, second paragraph,

under 35 U.S.C. § 102(b) and under 35 U.S.C. § 103(a). Each of these rejections is addressed in turn below in the order set forth by the Examiner.

Rejection of Claim 44 under 35 U.S.C. § 112, First Paragraph

Claim 44 has been rejected under 35 U.S.C. § 112, first paragraph as allegedly non-enabled. In making the rejection, the Examiner alleges that the claims cover a genus of mutants, *i.e.* mutants of CHA255, which are not enabled by the disclosure of the specification as filed. Applicants respectfully traverse this rejection.

A particular claim is enabled by the disclosure in an application if the disclosure, at the time of filing, contains sufficient information so as to enable one of skill in the art to make and use the claimed invention without ***undue*** experimentation. *See, e.g., In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988), or MPEP §2164.01. It is important to note that the possibility that some experimentation, even if such experimentation is complex or extensive, may be required for the practice of the invention does not necessarily mean that the invention is not enabled:

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See*, MPEP § 2164.01.

As explained above, the presently claimed invention is directed to a mutant antibody comprising a reactive site not present in the wild-type of said antibody and complementarity-determining regions (CDRs) that recognize a metal chelate. The reactive site is in a position proximate to or within said complementarity-determining regions. The reactive site is the mutation and has complementary reactivity with a reactive group on the metal chelate.

Applicants respectfully assert that there is ample guidance in the specification for one of skill in the art to make the claimed mutant antibodies without undue experimentation.

As explained in the Declaration of Dr. Meares, the specification describes multiple methods of generating the claimed mutant antibodies using methods known in the art (*see, e.g.*, specification at page 23, line 20 to page 50, line 9 and Declaration ¶7 (a-c)). For example, the specification explicitly sets forth art recognized methods of generating the claimed mutant antibodies (*e.g.*, site directed mutagenesis, PCR mutagenesis, and cassette mutagenesis);

multiple reactive sites that can be introduced into the mutant antibodies (*e.g.*, cysteinyl residues, histidyl residues, lysinyl and other amino terminal residues, arginyl residues, tyrosyl residues, aspartyl residues, glutamyl residues, glutaminyl residues, asparaginyl residues, proline residues, and lysine residues); and multiple metal chelates with reactive groups with complementary reactivity to the reactive site on the mutant antibodies (*see*, specification at page 23, line 20 to page 46, line 28; page 47, line 16 to page 48, line 26; page 61, line 25 to page 64, line 24; and Declaration ¶ 7(a)). Moreover, as Dr. Meares explains, the specification provides two working examples that describe generation of a CHA255 mutant, including identification of a suitable methods of identifying suitable placement of the mutation (*i.e.*, reactive site) in the CHA255 antibody, mutagenesis of the CHA255 antibody to incorporate the reactive site, expression of the mutant CHA255 antibody comprising the reactive site not present in the wild type CHA255; and irreversible binding of the mutant antibody to a metal chelate with a reactive group of complementary reactivity to the reactive site on the antibody (*see,* specification at page 67, line 19 to page 75, line 5; and Declaration ¶7(b)). Therefore, the disclosure of the specification provides ample guidance for one of skill in the art to generate the claimed mutant antibodies.

In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 102(b)

Claims 1-3, 14, 16-19, 24, 42, and 44 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Stickney *et al.*, *Immunology* 79:1979-1983 (1982). Applicants respectfully traverse this rejection.

For a rejection of claims under § 102(b) to be properly founded, the Examiner must establish that a single prior art reference discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991), the Federal Circuit held that "anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference . . . ***There must be no difference between the claimed invention and the reference disclosure, as***

viewed by a person of ordinary skill in the field of the invention." *Id.* at 1010 (emphasis added). Anticipation can be found, therefore, only when a cited reference discloses ***all*** of the elements, features or limitations of the presently claimed invention.

As explained above, in the Declaration of Dr. Meares, the present invention is directed to a mutant antibody comprising: (1) a reactive site not present on the wild type antibody, and (2) a CDR that specifically binds to a metal chelate (*see*, Declaration ¶4). The reactive site is the mutation and interacts with a reactive group on the metal chelate selected from carboxyl groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups.

In making this rejection, the Examiner has alleged that Stickney *et al.* teaches a mutant antibody because the (Fab')2 of Stickney comprises the binding sites of two different antibodies.

As defined in the specification and explained in the Declaration of Dr. Meares, a mutation is a substitution, addition, or deletion in a nucleotide encoding a polypeptide of interest (*see*, specification at page 23, lines 26-28; and Declaration ¶5). The antibody of Stickney *et al.* is generated by ***chemically*** linking the binding sites of two separate antibodies.. Thus, in contrast to the presently claimed mutant antibody, the antibody of Stickney *et al.* is not generated by a substitution, addition, or deletion in a nucleotide encoding the antibody. As Dr. Meares points out, Stickney *et al.*, contains no disclosure of generating a mutant antibody by introducing substitutions, additions, or deletions into the nucleotide encoding the antibody (*see*, Declaration ¶5). Therefore, Stickney *et al.* does not describe every element of the presently claimed invention and does not anticipate the claimed mutant antibody comprising a reactive site that is not present in the wild type of the antibody, wherein reactive site is the mutation, as disclosed and claimed in the present invention. Thus, an element of the presently claimed invention is absent from the disclosure of Stickney *et al.*

In view of the foregoing, Applicants respectfully submit that since Stickney *et al.*, does not disclose ***all*** of the elements, features or limitations of the presently claimed invention,

Stickney *et al.*, cannot form the proper basis for a § 102(b) rejection and respectfully request withdrawal of this rejection.

Rejections under 35 U.S.C. § 103(a)

Claims 1-3, 14, 16-20, 22-23, 25, 30-34, 37-38, 42-43, and 44 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Reardan *et al.*, *Nature* 316:265-267 (1985) and further in view of Orlandi *et al.*, *Proc. Nat'l. Acad. Sci. USA* 86:3833-3837 (1989), Pastan *et al.* (U.S. Patent No. 5,747,654), and Goodwin *et al.*, *J. Nucl. Med.* 29:226-234 (1988). Applicants respectfully traverse this rejection.

As set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met. *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. As explained herein below, Applicants assert that a *prima facie* case of obviousness has not been established because the cited references do not teach or suggest all the claim limitations. Moreover, one of skill in the art would have no motivation to combine the cited references. Finally, even if the disclosures of the cited references were combined, the combination would not lead to the presently claimed invention.

As explained above, and in the Declaration of Dr. Meares, the present invention is directed to a mutant antibody comprising: (1) a reactive site not present on the wild type antibody, and (2) CDRs that specifically bind to a metal chelate (*see*, Declaration ¶4). The reactive site is in a position proximate to or within the complementarity determining regions. The reactive site is the mutation and interacts with a reactive group on the metal chelate selected from carboxyl groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups.

The Examiner has previously acknowledged that Reardan *et al.* does not teach a mutant antibody comprising a reactive site that is not in the wild-type antibody (*see, e.g.*, Office Action mailed January 15, 2003). In the present Office Action, the Examiner does not discuss either Reardan *et al.* or Orlandi *et al.*, but alleges that Pastan *et al.* teaches a disulfide stabilized antibody comprising an SH group not present in the wild type antibody and that Goodwin *et al.* teaches a metal chelate comprising a reactive functional group of complementary reactivity to a reactive site. The Examiner concludes that the claimed mutant antibodies are obvious in view of the cited references because it would have been obvious to stabilize the antibody of Goodwin *et al.* using the methods of Pastan *et al.*

Applicants note that the Examiner alleges that Applicants' prior arguments were directed to the cited references separately while the rejection was based on the combination of references. Applicants respectfully submit that prior to a discussion of the combination of references, the disclosure of each reference must be addressed. Accordingly, in submitting this response, Applicants first address the deficiencies in the individual references, then follow this discussion with arguments regarding the references in combination.

The Combination of References Fails to Disclose Each Element of the Applicant's Claimed Invention

As explained above and by Dr. Meares, the present invention is directed to a mutant antibody comprising: (1) a reactive site not present on the wild type antibody, and (2) CDRs that recognizes a metal chelate (*see*, Declaration ¶4). The reactive site is in a position proximate to or within the complementarity determining region. The reactive site is the mutation and interacts with a reactive group on the metal chelate selected from carboxyl groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups. Applicants respectfully assert that the combination of the references does not disclose or suggest all of the elements of the present invention.

As explained by Dr Meares, the corresponding author of Reardan *et al.*, Reardan *et al.* discloses generation of ***wild type*** monoclonal antibodies specific for the EDTA chelate of indium, but contains no disclosure of any ***mutant*** antibodies (*see*, Declaration ¶ 6(a)(i)).

Also as explained by Dr. Meares, Orlandi *et al.* discloses amplifying the wild type variable regions of antibodies, but does not disclose or suggest any ***mutant*** antibody (*see, e.g.*, Declaration ¶6(a)(ii)).

In addition, Dr. Meares explains that Pastan *et al.* describe a polypeptide comprising two separate variable regions of a ligand binding moiety connected through a disulfide bond (*see, e.g.*, Declaration ¶6(a)(iii)). Pastan *et al.* contains no disclosure or suggestion that a reactive site on a mutant antibody may be in a location that would allow that reactive site to react with a reactive group on a metal chelate. As Dr. Meares notes, the disclosure of Pastan *et al.* does not even contain the term "metal chelate" (*see*, Declaration ¶ 6(a)(iii).

Finally, Dr. Meares, also an author of Goodwin *et al.*, explains that Goodwin *et al.* discloses ***wild-type*** monoclonal antibodies that specifically recognize and bind to a 1,4, dithiol spacer group of a metal chelate (*see, e.g.*, Declaration ¶6(a)(iv)). There is no reactive site on the antibodies of Goodwin *et al.* and, contrary to the Examiner's allegation, none of the compounds shown in Figure 1 of Goodwin *et al.* comprise a reactive group of complementary reactivity to the absent reactive site (*see id.*).

Thus, as Dr. Meares has explained, an element of the claimed invention is absent from each of the cited references (*see*, Declaration ¶6(a)(i-iv)). Specifically, none of the cited references discloses or suggests a mutant antibody that comprises a reactive site not present on the wild type antibody wherein the reactive site is the mutation and the reactive site reacts with a reactive group on a metal chelate. In the absence of a disclosure or suggestion of each claimed element, a proper *prima facie* case of obviousness has not been set forth. As explained in detail below, even if the references were combined, the combination would not lead to the claimed invention.

One Of Skill In The Art Would Have No Motivation To Combine The Cited References

As Dr. Meares explains, none of the cited references provide any motivation for one of skill in the art to generate mutant antibodies which comprise a reactive site which interacts with a reactive group on a metal chelate (*see*, Declaration ¶6(a)(i-iv)). In particular, Dr.

Meares points out that Reardan *et al.*, Orlandi *et al.*, and Goodwin *et al.* all describe ***wild-type*** antibodies (*see*, Declaration ¶6(a)(-iv) 6(b). None of these references disclose or suggest any mutant antibody, much less a mutant antibody that has a mutation that is a reactive site with complementary reactivity with a reactive group on a metal chelate (*see id.*). Dr. Meares also points out that Pastan *et al.* contains disclosure or suggestion that the disulfide linkage is positioned in a location where it may interact with a reactive group on a metal chelate bound to an antibody (*see*, Declaration ¶ 6(b)). Thus, as explained by Dr. Meares, none of cited references provides any catalyst that would motivate one of skill in the art to combine the references. In the absence of any mention or suggestion that the methods may be combined, the skilled artisan would not be motivated to make such a combination.

Moreover, as discussed below, even if the cited references were combined, the combination would not lead to the presently claimed mutant antibody comprising a reactive site not present on the wild type antibody wherein the reactive site is the mutation and the reactive site has complementary reactivity to a reactive group on a metal chelate.

One Of Skill In The Art Would Have No Reasonable Expectation of Success in Producing the Claimed Antibody by Modifying the Cited References

As explained by Dr. Meares, one of skill in the art would have no reasonable expectation of success in modifying the disclosures of the references to produce the claimed mutant antibody having mutation that is a reactive site that interacts with a reactive group on the metal chelate (*see*, Declaration ¶ 6(c)). Dr. Meares further clarifies that without the guidance in the specification regarding placement of the reactive site on the claimed mutant antibody, one of skill in the art would not have expected that modification of the cited references would successfully produce the claimed antibody (*see*, Declaration ¶ 6(c)). Moreover, as previously discussed, Pastan *et al.* contains no suggestion that a reactive group on a mutant antibody may be placed in a location that would allow the reactive site on the antibody to react with a reactive group on a metal chelate bound by the antibody. The Examiner has noted in response to the characterization of Pastan *et al.*, that the present claims do not clearly recite that the reactive site of the mutant antibody interacts with the reactive group on a metal chelate. Therefore, in

accordance with the Examiner's suggestion, the claims have been amended for clarity to recite that the reactive site on the antibody reacts with a reactive group on the metal chelate.

The Rejection of Claims 17 And 31 as Allegedly Reading on the Art

In making this rejection, the Examiner maintains that claims 17 and 31 are interpreted to mean that the targeting moiety can be the same as the antibody and alleges that the cited art reads on claims 17 and 31. Applicants respectfully disagree and submit that it is clear from the claims and the specification that the targeting moiety is distinct from the antibody and that the antibody and the targeting agent are two separate moieties that are linked together. However, solely to expedite prosecution, claims 17 and 31 have been amended to recite that the antibody and the targeting moiety are not the same. Therefore, withdrawal of this aspect of the rejection is respectfully requested.

In view of the foregoing remarks, Applicants respectfully submit that the present invention is non-obvious and patentable over Reardan *et al.*, further in view of Orlandi *et al.*, Pastan *et al.*, and Goodwin *et al.* Accordingly, Applicants urge the Examiner to withdraw this rejection under 35 U.S.C. § 103(a).

Rejections under 35 U.S.C. § 112, Second Paragraph

Claim 15 is rejected under 35 U.S.C. § 112, as allegedly infinite. In particular, the Examiner has alleged that it is unclear whether the serine 95 cysteine substitution is the mutation. In accordance with the Examiner's suggestion, claim 15 has been amended solely for clarity to recite that the serine 95 cysteine substitution ***is*** the mutation.

In view of the foregoing amendments and remarks, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 14-25, 30-38, and 42-44 are rejected under 35 U.S.C. § 112, first paragraph as allegedly non-enabled. In making this rejection, the Examiner acknowledges that that claims are enabled for a mutant antibody that comprises a reactive site that is the SH group

of cysteine and wherein the reactive site is proximate to the CDR, but alleges that the specification is not enabling for (1) a mutant antibody that contains ***any*** reactive site; or (2) a mutant antibody with the reactive site in the CDR.

As explained above, particular claim is enabled by the disclosure in an application if the disclosure, at the time of filing, contains sufficient information so as to enable one of skill in the art to make and use the claimed invention without ***undue*** experimentation. *See, e.g., In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988), or MPEP §2164.01. It is important to note that the possibility that some experimentation, even if such experimentation is complex or extensive, may be required for the practice of the invention does not necessarily mean that the invention is not enabled:

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See*, MPEP § 2164.01.

As explained above, the present invention is directed to a mutant antibody comprising: (1) a reactive site not present on the wild type antibody, and (2) CDRs that recognizes a metal chelate. The reactive site is in a position proximate to or within the complementarity determining region. The reactive site is the mutation and interacts with a reactive group on the metal chelate selected from carboxyl groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups.

As explained by Dr. Meares, there is ample guidance for one of skill in the art to practice the full scope of the claimed invention, *i.e.*, a mutant antibody comprising the claimed reactive sites proximate to ***or*** within the CDR of the antibody, wherein the reactive site is the mutation (*see*, Declaration ¶ 7). In particular, Dr. Meares points to the descriptions in the specification regarding (1) generation of mutant antibodies that recognize metal chelates; (2) multiple reactive sites that can be introduced into the mutant antibodies; and (3) multiple metal chelates with suitable reactive groups of complementary reactivity to the reactive site on the mutant antibodies, as specific guidance for one of skill in the art to practice of the claimed invention (*see*, specification page 23, line 20 to page 50, line 9; and Declaration ¶ 7(a)-(c)). Moreover, the specification provides actual working examples which further guide one of skill in

the art in the practice of the claimed invention by describing identification of a suitable position for placement of a mutation, *i.e.*, a reactive site, within the CDR of an antibody that specifically binds to a metal chelate, generation of a mutant antibody with a reactive site, and binding of the mutant antibody to a metal chelate with a reactive group with complementary reactivity to the reactive site (*see*, Declaration ¶ 7(a-c)). In particular, these portions of the specification demonstrate that the claimed reactive sites can be introduced as a mutation into an antibody and that the placement of the reactive site can be selected such that the reactive site is proximate to or within the CDR (*see*, Declaration ¶ 7(b-c)).

As pointed out by Dr. Meares, the specification describes multiple methods of generating mutant antibodies using methods known in the art (*see*, specification page 23, line 20 to page 50, line 9; and Declaration ¶7 (a-c)). For example, the specification explicitly sets forth art recognized methods of generating the claimed mutant antibodies (*e.g.*, site directed mutagenesis, PCR mutagenesis, and cassette mutagenesis); multiple reactive sites that can be introduced into the mutant antibodies (*e.g.*, cysteinyl residues, histidyl residues, lysinyl and other amino terminal residues, arginyl residues, tyrosyl residues, aspartyl residues, glutamyl residues, glutaminyl residues, asparaginyl residues, proline residues, and lysine residues); and multiple metal chelates with reactive groups with complementary reactivity to the reactive site on the mutant antibodies (*see*, specification page 23, line 20 to page 50, line 9; and Declaration ¶ 7(a)). Thus, based on the guidance in the specification, one of skill in the art would be able to practice the full scope of the claimed invention, *i.e.* to generate the claimed mutant antibodies that recognize a metal chelate and contain mutation that is the claimed reactive sites with complementary reactivity to a reactive group on the metal chelate, wherein the reactive site is proximate to or within a CDR.

Moreover, as Dr. Meares explains, the specification provides two working examples that describe generation of a CHA255 mutant, including identification of a suitable methods of identifying suitable placement of the mutation (*i.e.*, reactive site) in the CHA255 antibody, mutagenesis of the CHA255 antibody to incorporate the reactive site, expression of the mutant CHA255 antibody comprising the reactive site not present in the wild type CHA255; and irreversibly binding of the mutant antibody to a metal chelate with a reactive group of

complementary reactivity to the reactive site on the antibody (*see*, specification page 71, line 1 to page 75, line 5; and Declaration ¶7(b)). In particular, Examples 3 and 4 describe generation of a mutant antibody of the invention using computer based design to choose a position for the reactive site proximate to or within the CDR such that the reactive site (1) has suitable proximity to the reactive group on a metal chelate when the metal chelate is bound to the antibody; and (2) does not interfere with the interaction between the antibody and the metal chelate. Therefore, the disclosure of the specification provides ample guidance for one of skill in the art to generate the claimed mutant antibodies that recognize a metal chelate and contain mutation that is a reactive site with complementary reactivity to a reactive group on the metal chelate, wherein the reactive site is proximate to or within a CDR.

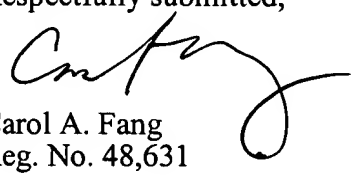
In view of the foregoing amendments and remarks, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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